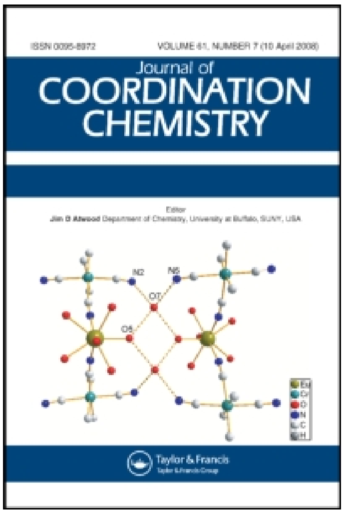

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MODEL COMPOUNDS THAT MIMIC COUPLED BIMUCLEAR COPPER PROTEINS AND ENZYMES. COPPER(I) COMPLEXES OF N,N,N′,N′-TETRAKIS(2′-BENZOIMIDAZOLYL METHYL)-α,α′-(DIMETHYLENE AMINO)PYRIDINE

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A number of properties and reactions of a new kind of synthetic dicopper oxygen carrier $[Cu_2(PTB)]X_2$ (X = ClO_4^-, BF_4^- and Cl^-), where PTB is *N,N,N′,N′*-tetrakis (2′-benzoimidazolyl methyl)-α,α′-(dimethylene amino)pyridine, are similar to those of coupled binuclear copper proteins and enzymes to a significant extent. The carriers serve as an active site model to mimic hemocyanin and tyrosinase. $[Cu_2\ (PTB)]^{2+}$ reacts very easily with O_2 and dioxygen adducts have been isolated. Colourless solutions of $[Cu_2(PTB)]^{2+}$ in dimethyl formamide (DMF) show a total absence of absorption in the near ultraviolet and visible region, but with oxygen give a blueish solution with characteristic, multiple absorptions at 320–390, 430 and 535 nm as well as fluorescence emission spectra (ex = 305 nm, em = 360–375, 410–420 nm). With addition of ascorbic acid, the solutions decolourize, the oxy-deoxy cycle can be repeated several times. ESR spectra of $[Cu_2(PTB)O_2]^{2+}$ in frozen DMF solution show an axial spectrum around g = 2 (Δms = ±1 transition) and g = 4.2 (Δms = ±2 transition), which can be interpreted as arising from a pair of magnetically coupled Cu(II) ions.

KEYWORDS: *N,N,N′,N′*-tetrakis(2′-benzoimidazolyl methyl)-α,α′-(dimethylene amino)pyridine, binuclear copper

INTRODUCTION

In so-called "Type III" or "ESR-silent" copper proteins and enzymes like hemocyanin (Hc) and tyrosinase (Tyr) as well as multi copper oxidases, such as laccase, ascorbate oxidase and ceruloplasmin, the active site in the oxidized form is generally thought to contain a pair of antiferromagnetically coupled copper ions,

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which are predominantly coordinated by the imidazole groups of histidines. Coordination geometry is known to influence specific properties. To help elucidate the structure and function of these copper proteins and enzymes, coordination compounds with less complicated ligand systems are studied as models. This paper reports that the synthesis and properties of dioxygen adducts of copper(I) with a new dinucleating ligand, *N,N,N′,N′*-tetrakis(2′-benzoimidazolyl methyl)-α,α′-(dimethyl amino)pyridine (PTB), $[Cu_2(PTB)O_2]X_2$ ($X = ClO_4^-$, BF_4^-, Cl^-).

EXPERIMENTAL

Chemicals and Apparatus

All chemicals were of commercially available reagent grade and were used without further purification. NMR spectra were measured on an XL-200E spectrometer. Chemical shifts are reported relative internal standard Me_4Si. IR spectra of solid compounds were recorded on a Perkin Elmer 983 spectrophotometer in the range 200–4000 cm^{-1}. The samples were either pelleted in KBr (for the ligand) or CsI (for complexes). No indications of decomposition in the KBr and CsI pellets were observed. Electronic spectra (190–900 nm) were obtained in DMF solution using a Shimadzu UV-Vis 265 spectrometer. ESR spectra at X-band frequencies were obtained with a JES-FEIXG spectrometer using frozen DMF solution at liquid nitrogen temperatures. A cylindrical quartz sample tube was used for the frozen samples. Spectra were calibrated against Mn^{2+} in MgO. Copper analyses were carried out by the diantipyl methane-sulforhodanide method. All other analyses were performed with a Perkin Elmer 2400 analyzer. Fluorescence spectra were obtained with a RF-540 luminescence spectrophotometer.

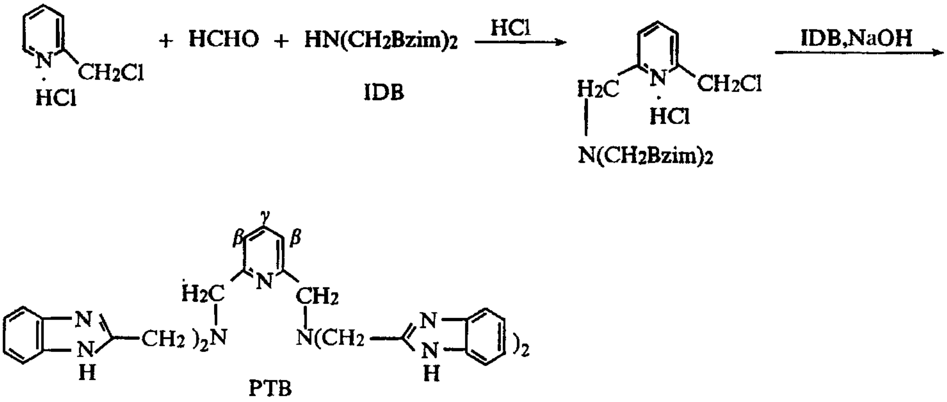
Synthesis of N,N,-di(2′-benzoimidazolyl methyl)imide (IDB)

All ligands containing benzoimidazole groups can be obtained by general methods.[1-3] IDB was prepared by the following procedure, 1,2-diaminobenzene and imido-diacetic acid were finely ground together in a 2:1 mol ratio and heated at 140–180°C until no more water vapour evolved. After cooling, the resulting dark red glass was dissolved in hot ethanol (containing charcoal) and filtered. Additions of water induced crystallization. The crude product was recrystallized from $EtOH\text{-}H_2O$. A white powder was obtained, $HN(CH_2Bzim)_2$; ^1H NMR (CD_3OD, TMS) δ: 7.65 (m,4H), 7.25 (m,4H), 4.50 (S,4H).

Synthesis of PTB

2-Picolylchloride hydro-chloride, formadehyde and *N,N*-di(2′-benzoimidazolyl-methyl)imide were reacted in a 1:1:2 mol ratio in ethanol (catalyzed by hydrochloric acid) at 50–60°C. After 48 hours, excess NaOH (4.0g) was added and the reaction continued for 72 h. The solvent was removed to give a white solid. The filtered precipitate was washed by slurrying in water than with diethyl ether a few times. The PTB obtained was dried in vacuum at 50°C; ^1H and ^{13}C NMR spectra (DMSO-d_6): 8.56 (t,1H), py-γH; 7.95 (t,2H), py-βH; 12.60 (s,4H), Bzim-NH; 7.55 (m,8H), 7.15 (m,8H), Bzim-H; 4.15 (s,8H), Bzim-CH_2; 4.05 (s,4H), py-CH_2;

3.3–3.5 (br,H_2O); Ar-C: 154.86, 152.75, 151.49, 141.79, 135.76, 122.34, 121.59; 49.20, Bzim-methylene-c; 39.75, py-methylene-c. IR/cm^{-1} (KBr): 3166-2782 (br,s), Arv$_{N\text{-}H}$ and Arv$_{\text{-}C\text{-}H}$; 1439(vs), 1455(s), v_{CH_2}; 1273(s), $v_{\text{-}N=C}$; 729(vs) aromatic ring vibration. Electronic spectrum λmax/nm (εm/cm^{-1}M^{-1}); 245(24820), 272(27780),282(29630).



Synthesis and Characterization of Complexes $[Cu_2(PTB)O_2](ClO_4)_2\cdot 3H_2O$*(I)*

PTB (0.66 g, 1 mmol) was dissolved in 50 cm^3 of MeOH-CH_3CN (v/v = 4/1) and this solution was added dropwise with stirring to solid $[Cu(CH_3CN)_4]ClO_4$ (0.66 g, 2 mmol) under a nitrogen atmosphere. The solid initially dissolved after heating for a few minutes; with cooling, a fine off-white precipitate formed. The mixture was stirred for 4 h exposed to air at room temperature, when a greyish blue precipitate was obtained. This was filtered and washed with anhydrous methanol, acetonitrile and diethyl ether, then dried in vacuum. *Anal.* calcd. for $[Cu_2(C_{39}H_{35}N_{11})O_2](ClO_4)_2\cdot 3H_2O$: C, 43.78; N, 14.41; H, 3.27; Cu, 11.88%. Found: C, 43.56: N, 14.87; H, 3.51; Cu, 11.49%. Molar conductivity (DMF) Λm = 145 S cm^2 mol^{-1}. IR (CsI, cm^{-1}): 250(w), 282(w), $v_{Cu\text{-}N}$; 326(w), $v_{Cu\text{-}O}$; 873(m), $v_{O\text{-}O}$; 1100, ClO_4^-. Electronic spectrum (DMF), λmax/nm (ε_m/cm^{-1} M^{-1}): 276(36400), 280(35200), 320(sh, 3057), 430(300), 630(235). Fluorescence (DMF): ex = 305 nm, em = 370, 420 nm (sh). ESR: $g_\parallel$ = 2.279, $g_\perp$ = 2.097, g_h = 4.20, $A_\parallel$ = 172 × 10^{-4}T.

$[Cu_2(PTB)O_2]Cl_2\cdot 3HCl\cdot 3H_2O$ *(II)*

PTB (0.66 g, 1 mmol) in 50 cm^3 of MeOH saturated with HCl was added dropwise with stirring to solid CuCl (0.30 g, 3 mmol) under nitrogen. The resulting clear yellow solution was stirred for 4 h exposed to air at room temperature. A yellow-green powder was collected by filtration, washed with methanol and diethyl ether and dried in vacuum. *Anal.* calc. for $[Cu_2(C_{39}H_{35}N_{11})O_2]Cl_2\cdot 3HCl\cdot 3H_2O$: C,44.40; N,15.34; H, 4.25; Cu, 11.64%. Found: C, 44.55; N, 14.66; H, 4.19; Cu, 11.90%. Λm = 159 S cm^2 mol^{-1}. IR/cm^{-1}: 242 (w), 278 (w) $v_{Cu\text{-}N}$; 324 (w), $v_{Cu\text{-}O}$; 854(m) $v_{O\text{-}O}$. Electronic spectrum (DMF): λmax/nm (ε_m/cm^{-1}M^{-1}) 270(81761), 276(80503), 370(sh), 390 (sh), 430(1182), 535(72), 720 (340). Fluorescence. ex =

305 nm, em = 370 nm, 420 nm. ESR: $g_{\parallel} = 2.228$, $g_{\perp} = 2.103$, $g_h = 4.18$, $A_{\parallel} = 158 \times 10^{-4}$T.

$[Cu_2(PTB)O_2](BF_4)_2 \cdot HCl$ (III)

PTB (0.66g, 1 mmol) in 50 cm^3 of dry HCl saturated MeOH was added dropwise with stirring to a solid mixture of CuCl (3 mmol) and $NaBF_4$ (0.3 g, 3 mmol) under nitrogen. The solid initially dissolved with heating for 15 min. Upon cooling, a fine yellow-white precipitate formed. The suspension was stirred for 4 h exposed to air at room temperature. A yellow-green powder was obtained by filtration, washing and drying. *Anal.* calc. for $[Cu_2(C_{39}H_{35}N_{11})O_2](BF_4)_2 \cdot HCl$: C, 45.59; N, 15.00; H, 3.50; Cu, 12.37% Found: C, 45.54; N, 15.56; H, 3.35; Cu, 12.30% $\Lambda m = 156$ S cm^2 mol^{-1}. IR/cm^{-1} 275(w), 295(w) $\nu_{Cu\text{-}N}$; 324(w) ν_{Cu-O}; 852(m) ν_{O-O}, 1061(s) BF^-_4. Electronic spectrum (DMF) λmax/nm (ε_m/$cm^{-1}M^{-1}$): 270(32000), 276(30000), 280(22000), 350(876), 390(370), 430(790), 535(72), 720(182). Fluorescence: ex = 305 nm, em = 360 nm, 410 nm. ESR: $g_{\parallel} = 2.278$, $g_{\perp} = 2.089$, $g_h = 4.26$, $A_{\parallel} = 161 \times 10^{-4}$T.

RESULTS AND DISCUSSION

The complexes are soluble in DMF. Molar conductances of the complexes in DMF at a concentration of *ca* 10^{-3}M at 20°C are in the range 145–159 S cm^2 mol^{-1}, indicating bivalent behaviour in solution.[4]

Dioxygen adducts $[Cu_2(PTB)O_2]X_2$ ($X = ClO_4^-, BF_4^-, Cl^-$) with varying amounts of crystal water or HCl in DMF solution show a strong resemblance to spectra of hemocyanin, tyrosinase and so on. The complexes undergo a reversible colour change with added ascorbic acid and bubbling O_2 which can be followed by electronic and fluorescence spectrophotometer. The redox cycle can be repeated several times.

By comparison with the spectrum of the free ligand, the highest energy bands (<300 nm) are ascribed to intra-ligand, probably $\pi \rightarrow \pi^*$, transitions of aromatic groups. The broad lowest energy bands (630 and 700 nm) are undoubtedly ligand field transitions of the tetragonal copper(II) center. The most striking feature of the electronic spectra of $[Cu_2(PTB)O_2]^{2+}$ in DMF is the multiple band at 330, 350, 390 and 535 nm, which may be attributed to peroxide π^*_σ and π^*_v to copper(II) $d_{x2\text{-}y2}$ ligand to metal charge transfer; the 430 nm band may be responsible for LMCT from the aromatic tertiary amine N atom to Cu(II). The band position and intensity are consistent with data for other systems.[5] Addition of ascorbic acid to solutions of the complexes causes solutions rapidly to become colourless and the near ultraviolet-visible (> 300 nm) bands disappear with the formation of Cu(I). The electronic features observed are very similar to those observed for oxy-Hc and deoxy-Hc and oxy-Tyr and deoxy-Tyr.

The fluorescence emission spectra (excitation at 305nm) of all the complexes in DMF solution are due to a $\pi \rightarrow \pi^*$ transition (of aromatic groups). Fluorescence emission intensities (I) near 370 and 420 nm increase rapidly with added ascorbic acid and gradually decrease with bubbling O_2 or exposure to air (as shown in Figure 1). In other words, the dioxygen adducts show strong quenching of fluorescence with respect to deoxy-cuprous species, attributed to an energy transfer from aromatic

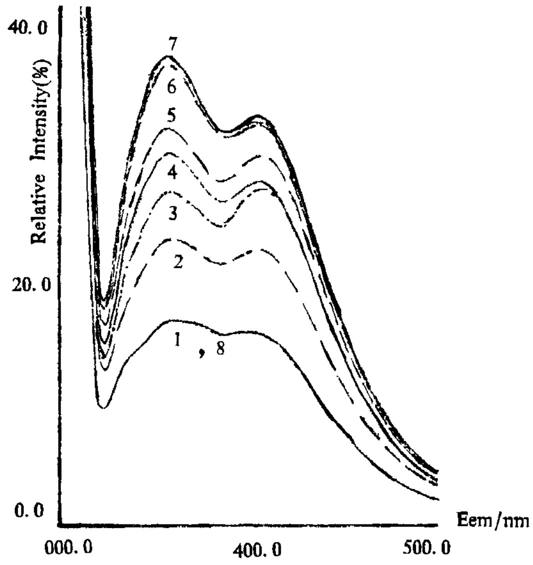


Figure 1 Fluorescence intensity changes for $[Cu_2(PTB)O_2](BF_4)_2 \cdot HCl$ upon adding ascorbic acid: fluorescence intensity of a 2.22×10^{-4} mol dm^{-3} $[Cu_2(PTB)O_2](BF_4)_2 \cdot HCl$ DMF solution in the absence (curve 1) and presence of 3.30×10^{-4} (curve 2), 6.50×10^{-4} (curve 3), 1.26×10^{-3} (curve 4), 1.82×10^{-3} (curve 5), 2.30×10^{-3} (curve 6), 2.83×10^{-3} mol dm^{-3} (curve 7) ascorbic acid. Curve 8 is obtained after exposing the solution of curve 7 to air.

groups to O_2-Cu(II) species; the fluorescence of all complexes decrease and show strong quenching as compared with the free ligand. This feature is similar to that of oxy-Hc or oxy-Tyr and deoxy-Hc or deoxy-Tyr (or in place of CO).[6]

The dioxygen adducts give axially symmetric ESR spectra in frozen DMF solution; $g_{\parallel} > g_{\perp} > g_e$ (2.0023, free electron value) implies that the unpaired electron of the copper(II) complexes reside in the $d_{x2\text{-}y2}$ orbital. All dioxygen adducts show $g_{\parallel} < 2.3$, indicating that the complexes possess considerable covalent character (it should be noted that for an ionic environment $g_{\parallel} > 2.3$).[7] At lower magnetic field, a parallel hyperfine structure with a four-line splitting pattern of the copper nucleus is more clearly resolved. The half-field signal at *ca* 1600 G (1 G = 10^{-4} T) also is clearly seen. This shows that the copper complexes are dinuclear, with antiferromagnetic interaction between two Cu(II) nuclei. Addition of sufficient ascorbic acid results in a completely decolourized solution which is completely ESR-silent. Oxy-Hc is ESR-silent because there is a strong antiferromagnetic coupling between the two Cu(II) ions with a separation close to 3.6 Å. ESR spectra of the $[Cu_2(PTB)O_2]^{2+}$ ion, unlike oxy-Hc, have a characteristic signature with normal $g_{\parallel}$, $g_{\perp}$ and $A_{\parallel}$. This suggests that the distance between the two copper ions is probably > 4 Å and < 7 Å.[8] A weak dipolar coupling, yielding a triplet state ESR resonance (binuclear signals) near g = 2, (ΔMs = ± 1) and g = 4 (ΔMs = ±2), is similar to ESR-detectable met-Hc, or so-called "dimer-Hc". The $g_{\parallel}/A_{\parallel}$ ratio can be used as the criterion for the assumed departure from planar geometry.[9] A value of 105–135 corresponds to square-planar. The 136–200 range is representative of a tetrahedral environment. The $g_{\parallel}/A_{\parallel}$ ratio of the dioxygen complexes I–III in frozen DMF is in the region of 133 (for I), and 141 (for II, III), which suggests that the copper(II) ions may be in a distorted tetragonal pyramidal environment. From electronic and IR spectro-scopy, it is established that dioxygen is bound as μ-peroxide ($\nu_{O-O} = 852$–$873\ cm^{-1}$). The coordination geometry around each copper(II) ion may be described as a distorted tetragonal pyramid[10] with two equatorial benzimidazole nitrogen atoms, one amine nitrogen atom and one oxygen atom of the peroxide bridge as well as one axial pyridyl nitrogen.

Acknowledgement

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